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infectio

REVIEW

Histoplasmosis: An endemic mycosis. Overview of epidemiology, clinical features, diagnosis, and treatment

Michael Muñoz-Rosa[1,*], Nicolas Rhyman[2], Ángela María Tobón-Orozco[3]

Abstract

Histoplasmosis is an endemic fungal disease in America caused by a dimorphic fungus, *Histoplasma capsulatum*, which affects immunocompetent individuals and, more significantly, those with immune system impairments or at the extremes of age. Children are particularly susceptible to disseminated disease and severe forms, with high lethality if left untreated. The most common symptoms include fever, weight loss, and visceromegaly, although the disease can often be completely asymptomatic, depending on host factors and the initial inoculum size. Histopathology, antigen and antibody measurement, culture, and molecular techniques are fundamental in diagnosing histoplasmosis, with varying effectiveness across different clinical forms. When treatment is indicated, international guidelines recommend intensive induction therapy with Amphotericin B for 2 to 4 weeks, followed by itraconazole for 12 months as maintenance therapy in disseminated forms. Follow-up should ensure clinical and microbiological cure and a decrease in antigenuria levels to prevent relapse and ensure therapeutic success.

Keywords: Histoplasmosis*; Histoplasma capsulatum*; fungal diasease

Histoplasmosis: Una micosis endémica. Visión general de la epidemiología, características clínicas, diagnóstico y tratamiento

Resumen

La histoplasmosis es una enfermedad fúngica endémica en América causada por un hongo dimórfico, *Histoplasma capsulatum*, que afecta a individuos inmunocompetentes y, de manera más significativa, a aquellos con déficits en el sistema inmunológico o en los extremos de la edad. Los niños son particularmente susceptibles a la enfermedad diseminada y a formas severas, con alta letalidad si no se tratan. Los síntomas más comunes incluyen fiebre, pérdida de peso y visceromegalia, aunque la enfermedad puede ser completamente asintomática, dependiendo de factores del huésped y del tamaño del inóculo inicial. La histopatología, la medición de antígenos y anticuerpos, el cultivo y las técnicas moleculares son fundamentales en el diagnóstico de la histoplasmosis, con eficacia variable en las diferentes formas clínicas. Cuando se indica tratamiento, las guías internacionales recomiendan una terapia de inducción intensiva con anfotericina B durante 2 a 4 semanas, seguida de itraconazol durante 12 meses como terapia de mantenimiento en formas diseminadas. El seguimiento debe asegurar la cura clínica y microbiológica y una disminución de los niveles de antigenuria para prevenir recaídas y garantizar el éxito terapéutico.

Palabras claves: Histoplasmosis, *Histoplasma capsulatum,* enfermedad fúngica.

Introduction

Histoplasmosis, also known as Darling's disease or cave disease, is a systemic mycosis first described by Samuel Taylor Darling in 1905 in the Panama Canal area during the autopsy of an Afro-American individual whose tissues revealed encapsulated intracellular microorganisms in histiocytes. Darling considered these to be protozoa and named them *Histoplasma capsulatum*. In 1906, he defined it as a new disease after observing these intracellular microorganisms in two individuals with splenomegaly[1].

It was not until 1913 that the Brazilian researcher Henrique da Rocha-Lima concluded that histoplasmosis was a mycosis and not a protozoan disease. In 1929, Katherine Dodd and Edna Tomkins described the first in vivo pediatric case in a 6-month-old infant[1].

This disease is endemic in the Americas, ranging from Canada to Argentina. These regions are rich in river valleys and provide a suitable habitat for this microorganism. Taxonomically, *Histoplasma capsulatum* belongs to the kingdom Eumycota, division Ascomycota, class Euascomycetes, order Onygena-

1 Division of Pediatric Infectious Diseases, Department of Pediatrics, CES University, Medellin, Colombia. https://orcid.org/0009-0000-3628-041X
2 Hospital Sant Joan Despí Moisés, Broggi, Barcelona, España. https://orcid.org/0009-0008-2216-0140
3 Colombian Institute of Tropical Medicine – ICMT, CES University, Medellín, Colombia. https://orcid.org/0001-8305-7755
* Autor para correspondencia:
Correo electrónico: munoz.michael@uces.edu.co

Recibido: 26/09/2024; Aceptado: 04/12/2024

Cómo citar este artículo: M. Muñoz-Rosa, *et al.* Histoplasmosis: An Endemic Mycosis. Overview of Epidemiology, Clinical Features, Diagnosis, and Treatment. Infectio 2025; 29(2): 106-116

les, and family Onygenenaceae. The prevalence of infection is as high as 80% of the population in hyper-endemic areas, such as the Ohio and Mississippi river valleys, as well as in the southeastern states of the United States[2].

The fungus forms mycelia at ambient temperature, with microconidia found in soils enriched with bird and bat droppings and in construction debris. Infection is acquired through the inhalation of microconidia and is not transmitted from person to person or from person to animal. In over 90% of cases, the disease is asymptomatic or manifests as an acute, self-limiting symptomatic form. A small percentage (5%) of patients developed a subacute symptomatic pulmonary form, which was more likely to be diagnosed. Chronic pulmonary or progressive disseminated forms may also occur depending on the patient's clinical characteristics[3].

Children exposed to the fungus have high rates of mild or asymptomatic infection, but those under two years old are at the highest risk of severe disease, which can be directly proportional to the inoculum size or occur in the presence of primary or acquired immunodeficiency, particularly impaired T-cell function[4, 5, 6].

Ávila et al. in Panama established that the most important risk factor in older children is immunosuppression from any cause, while in younger children, malnutrition, hematologic-oncologic disease, or merely immune system immaturity may be the key factors[5].

Materials and methods

For this narrative review, a search was conducted for scientific articles (RCTs) and review articles published between 1971 and 2024 in the EMBASE and PUBMED databases. The following MeSH terms were used: histoplasmosis, *Histoplasma capsulatum*, disseminated histoplasmosis, *Histoplasma* infection, epidemiology, clinical manifestations, diagnosis of histoplasmosis, treatment, and follow-up. The search included articles in Spanish and English.

Epidemiology

Histoplasmosis is considered the most common endemic respiratory mycosis globally, predominantly in the Americas. It is not a notifiable disease, leading to significant underreporting, which poses a major limitation in establishing public health policies[1,2,5,7].

The most important endemic areas are located in the Americas, specifically in the Ohio and Mississippi River valleys. The disease also extends through southern Mexico, Central America, and South America, and reaches the central valley of Argentina. Other endemic regions were found on African and Asian continents. It is estimated that 40 million individuals are affected, with an annual incidence of 200, 000 new cases in endemic areas. However, this may be an underestimation because of the number of asymptomatic cases and the scarcity of reports from low-resource areas, such as the African continent. In parts of North America, such as Cincinnati, Ohio, Illinois, and Missouri, 80% of the population aged 20 years exhibits a positive histoplasmin skin test[2,5].

In Colombia, a study conducted by Dr. Cardona identified an average of 22% H. capsulatum infections in different areas of the country[8]. In Africa, *H. capsulatum* is primarily found in caves in East, South, and West Africa. In these regions, it is difficult to establish the prevalence of the disease owing to the unavailability of diagnostic tests in many areas[9].

In Argentina, a high prevalence of histoplasmosis has been documented in certain areas of the northwest, such as La Toma and Choromoro, where more than 30% of the individuals tested positive for histoplasmin skin tests, indicating a high level of endemicity[11]. Additionally, in Santa Fe, Argentina, a high incidence of histoplasmosis has been observed in renal transplant recipients, with a significantly higher prevalence than in other endemic areas[12].

In Brazil, histoplasmosis is common throughout the country, although its true burden is underestimated due to the lack of mandatory reporting[13]. A genetic study revealed high genetic diversity among Brazilian isolates of *Histoplasma capsulatum*, suggesting that Brazil may be a center of dispersion for this infection in South America[14].

In Mexico, significant genetic diversity has been identified among *Histoplasma capsulatum* isolates, suggesting the presence of recombinant populations. This may have implications for the epidemiology and control of this disease in the country[15].

Cases have been reported in some parts of Europe, such as Italy, France, Spain, and Germany, particularly in individuals who have recently traveled to endemic areas. However, autochthonous cases have been described in Italy[5,10,16,17].

Histoplasmosis affects men more than women, with a ratio ranging from 3:1 to 6:1, depending on the review. One of the factors contributing to this difference is occupational exposure, as the most common exposure environments include poultry farms, caves, or construction areas. There are multiple reports where exposure to bat and bird droppings is described in 70-80% of outbreaks, making it an important causal relationship of the infection and disease[1,4,5,18].

The disease can occur at any age but is more common at the extremes of life, such as in children or the elderly, and in immunocompromised patients, especially those with defects in cellular immunity, such as patients infected with HIV[1,5,19].

Histoplasmosis continues to be an invasive fungal disease that causes significant morbidity and mortality in HIV-infected patients in endemic areas. It becomes an AIDS-defining illness in 30-50% of the cases in some regions. Although an-

tiretroviral therapy has significantly reduced the incidence of this mycosis, mortality from progressive disseminated histoplasmosis (PDH) in HIV patients continues to rise in endemic areas, ranging from 23% to 33% in Colombia[19,20,21].

Etiopathogenesis

The causative agent of histoplasmosis is *Histoplasma capsulatum* (Darling 1906), of which three varieties are known: *H. capsulatum*; *H. duboisii* (Vanbreuseghem 1952), responsible for American and African histoplasmosis in humans; and *H. farciminosum* (Rivolta 1873; Weeks Padhye Ajello 1985), reported as a cause of disease in horses and mules in African regions. The *H. capsulatum* and *H. duboisii* varieties are identical strains, differing only in the absence of urease activity in the latter[1,5,22].

Sepúlveda et al. (2017) conducted a genome-wide population genetic analysis of *Histoplasma capsulatum* using 30 isolates representing four recognized regions where histoplasmosis is endemic. They found that the *genus Histoplasma is composed of at least four genetically isolated species.* Based on these findings, they proposed a new taxonomic classification, categorizing the fungus into four well-defined species: *Histoplasma capsulatum sensu stricto* Darling 1906 (previously known as the Panama or H81 lineage), *Histoplasma mississippiense* sp. nov. (formerly known as Nam 1), *Histoplasma ohiense* sp. nov. (formerly known as Nam 2), and *Histoplasma suramericanum* sp. nov. (formerly known as LAm A)[22].

Recently, molecular biology techniques have allowed the identification of eight clades geographically distributed as follows: Australia, the Netherlands, Eurasia, North American classes 1 and 2 (NAm 1 and NAm 2), Latin American groups A and B (LAm A and LAm B), and Africa. With the exception of the Eurasian cluster, these clades are considered phylogenetic species[23,24].

There is a significant difference among these clades: the South American varieties have a higher potential to cause skin lesions (37.8% in Colombia) compared to the North American clades, which show lower involvement (1-7% in the USA) [1,27 30].

The reservoir of *H. capsulatum* is found in soil, which is rich in nitrogen and phosphorus and is contaminated by bird and/or bat guano in tropical or subtropical climates. Bats carry the fungus in their gastrointestinal tract, while birds carry it on their feathers and are unaffected by their high body temperature[1,5].

In the environment, the fungus exists in its saprophytic or mycelial form with conidia that are inhaled by the host. There are two types of conidia: macroconidia, measuring 8–15 µm in diameter, and microconidia, measuring 2–5 µm in diameter. The latter are small enough to reach the alveoli, where, at a temperature of 37°C, they transform into yeast (the pathogenic phase), are phagocytosed by macrophages, and reach the mononuclear phagocytic system[26]. Conidia in the alveoli bind to a family of proteins called integrins (CD11 and CD18); therefore, this transformation may occur intracellularly. Multiple fungal genes that mediate growth and transition from the mycelial form to the yeast form have been identified, including Ryp1, Ryp2, and Ryp21[26,27].

The incubation period of infection lasted between 5 and 18 days, depending on the inoculum size. Phagocytosed microorganisms undergo rapid hematogenous dissemination and can be observed in the spleen, bone marrow, lymph nodes, liver, and adrenal glands. The infection is usually self-limiting due to the action of the immune system, but it can leave calcifications in the lungs, liver, and spleen, hypersensitivity to the antigen (histoplasmin), and the presence of antibodies against *H. capsulatum*. After 2–3 weeks, specific cell-mediated immunity develops, and macrophages are activated to kill microorganisms. Cytokines, including IL-12, interferon-gamma, and tumor necrosis factor-alpha (TNF-α), stimulate macrophages to eliminate the fungus and halt disease progression. Granulomas form in these fungal deposit sites, where the fungus can remain latent for a long time, leading to later reactivation in states of immunosuppression[1,26,27].

In the vast majority of cases, infection occurs in immunocompetent individuals, in whom symptoms are minimal and often asymptomatic, and the immune system adequately controls the infection. However, the intensity and clinical form that develop depend on the number of inhaled conidia, as well as the host's immune response and the integrity of the bronchial tree. When there is a deficiency in cellular immunity, the disease becomes progressive, and even a small inoculum can lead to severe infection with extensive dissemination. This scenario is common in immunocompromised individuals, children under two years of age, those undergoing prolonged corticosteroid therapy, anti-TNF-α therapy, solid organ or hematopoietic transplant recipients, and those with HIV infection[19].

Clinical Forms

Histoplasmosis can be clinically classified according to its anatomical location and temporality, based on the host's immunological scenario. The oldest and currently used classification was established in 1980 and 1981[3,28], which describes, in immunocompetent hosts, the acute or epidemic pulmonary form with symptoms lasting less than one month. However, this form is often undiagnosed or untreated. Currently, a subacute form with symptoms lasting more than one month is recognized, which often prompts the patient to seek medical attention, allowing for diagnosis and treatment[1,4].

In patients with pre-existing pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) or tuberculosis sequelae (cysts or bullae), *H. capsulatum* infection may lead to chronic pulmonary histoplasmosis, a condition similar to the clinical and radiological presentation of tuberculosis. In patients with immune system impairment, initial fungal dissemination is not controlled, leading to the most severe form, progressive disseminated histoplasmosis, which involves organs other than the lungs[29].

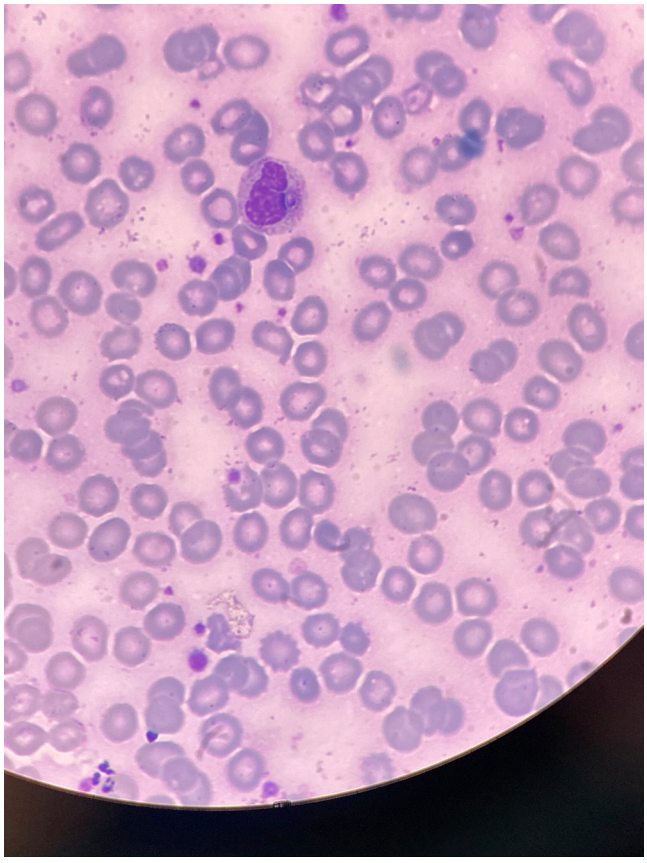

Figure 1. Wright-stained peripheral blood smear from a patient with progressive disseminated histoplasmosis. The image shows a yeast phagocytosed by a neutrophil, typical of *H. capsulatum*.

Acute Pulmonary Histoplasmosis

More than 90% of cases go unnoticed. The incubation period was approximately three weeks, but it depended on the size of the inoculum. In a healthy host, the most common presentation is a self-limited, asymptomatic infection or mild, nonspecific symptoms that resolve in less than two weeks. However, if the inoculum contains a large number of conidia, exposure can result in acute respiratory disease even in an immunocompetent person, showing a radiological pattern of reticular or reticulonodular interstitial infiltrate on chest X-ray, signs of nonspecific pneumonitis, the presence of granulomas, and hilar lymph node enlargement on computed tomography (CT)[5,29].

Granulomas may or may not calcify, and their formation requires an immune response involving TNF-α, IL-17, and IFN-δ, whose function is to contain the growth of the fungal structure. A lack of granuloma organization indicates an inadequate immune response and can lead to progressive fungal dissemination[4,27,30].

This symptomatic acute form is characterized by dry cough, fever, chills, chest pain, and fatigue, sometimes accompanied by erythema nodosum and arthralgia. Diagnosis is primarily established based on clinical and epidemiological findings, as laboratory tests are often negative in the early stages of primary infection. However, intradermal reactions (IDR) may be positive in 90% of cases. If symptoms persist for more than one month, it is considered a subacute pulmonary form, which has a higher likelihood of being diagnosed and treated promptly[4].

Antibodies against *H. capsulatum* are present in 60-85% of cases two weeks after infection, and direct examination and histopathology of respiratory secretions allow for diagnosis in only 10-20% of cases. Urinary antigen is positive in the acute form in 80% of cases but decreases to 30% in the subacute form, while antigenemia is positive in 75-82% of cases[4,5,31].

Acute pericarditis has been described in up to 5% of cases, and is explained by the acute inflammatory response generated in lymphoid and reticuloendothelial tissue secondary to extrapulmonary dissemination of the fungus[26, 31].

Acute Reinfection

It occurs in endemic areas of infected individuals that are repeatedly exposed to the fungus. The incubation period was shorter, with symptoms usually appearing during the first week of exposure, often resembling influenza infection[5].

Chronic Pulmonary Histoplasmosis

It is a chronic process that occurs in older patients, usually immunocompetent, with underlying pulmonary disease, and is exceptionally rare in children. It manifests as fatigue, fever, night sweats, weight loss, worsening of previous respiratory symptoms, dyspnea, cough with sputum production, and sometimes hemoptysis[1, 27, 32, 33].

This form has two presentations: cavitary and noncavitary. The cavitary form occurs in 39% of patients according to various studies and is radiologically characterized by the formation of cavities in the upper lobes in 98% of cases, with progressive fibrosis, a condition resembling tuberculosis[26]. The noncavitary form is characterized by nonspecific nodular infiltrates (Figure 2 and Figure 3) and hilar lymph node enlargement without other characteristic findings, with an initial diagnostic suspicion of a tumor or metastatic lesion[34].

During chronic infection with cavity formation, Wright, PAS, and Giemsa staining of bronchial lavage secretions were positive in 75% of cases, and cultures were positive in 67% of cases. The skin test (IDR) is positive in up to 70-90% of cases, and antibody titers against *H. capsulatum* were positive in 83% of cases, with titers greater than 1:16 in 75%. Urinary and bronchoalveolar lavage antigens were present in 88% of the patients. Combining several methods increases the diagnostic probability[31].

In approximately 20% of cases, cavitary lesions may recur after treatment, requiring prolonged treatment or a new course of antifungal therapy in cases of relapse. The response rate to pharmacological treatment is somewhat lower in the cavitary form than in the non-cavitary form[26, 35].

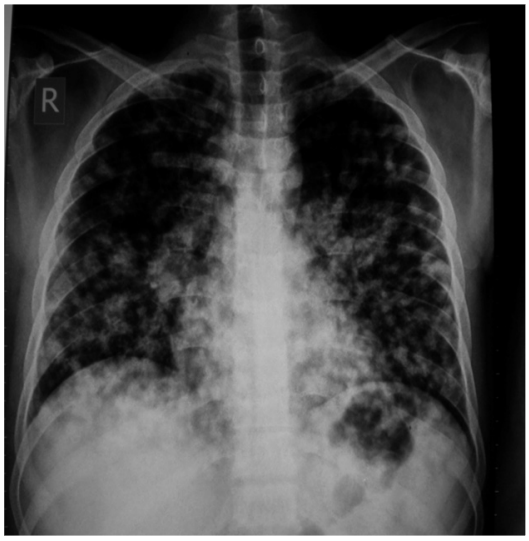

Figure 2. Chest X-ray of a patient with severe pulmonary histoplasmosis, showing diffuse nodular infiltration.

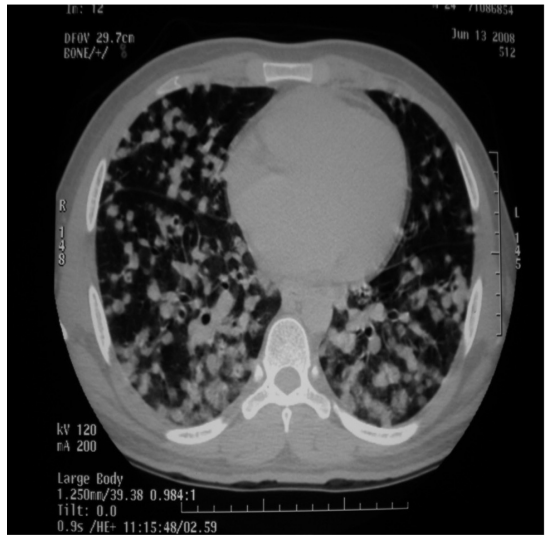

Figure 3. Chest computed tomography (CT) scan. Corresponding to the patient from Figure 2, showing multiple medium-sized nodules.

Complications of Pulmonary Histoplasmosis

They are very rare in healthy children or adults and generally occur in patients with structural lung alterations or as part of an exaggerated inflammatory response, such as granulomatous mediastinitis, characterized by excessive enlargement of the hilar lymph nodes, often with caseous necrosis and calcification. Patients may be asymptomatic or present with worsening of the previously described pulmonary symptoms, such as hemoptysis, chest pain, and dyspnea. Occasionally, calcified material from the lymph node rupture into the bronchi may be expectorated, a condition known as broncholitis[5,26].

Fibrosing mediastinitis is another rare inflammatory manifestation unrelated to granulomatous mediastinitis. This form involves an intense immune response characterized by chronic fibrosis, which is inappropriate and uncontrolled, affecting the infected lymph nodes. Fibrosis involves the airway and mediastinal vascular structures, a complication that does not respond to antifungal or steroid therapy, and requires stent placement to attempt clinical improvement[29, 36].

Progressive Disseminated Histoplasmosis

Understanding the pathogenesis of the disease, it is clear that in all cases, the infection spreads through lymphatic and hematogenous routes to the pulmonary lymph nodes and subsequently to the mononuclear phagocytic system and other organs, as macrophages constantly travel to and from the lungs. Given this assertion, we must apply the term "progressive," which means uncontrolled growth of the microorganism in organs other than the lungs[26,30].

This form occurs almost exclusively in immunocompetent children under two years of age as a progression of the initial pulmonary disease due to their immunological immaturity, in those with malnutrition or underlying hematologic-oncologic disease, in elderly adults due to senescence of the immune system, or in immunocompromised patients of any age, especially those infected with HIV and with a CD4 T-cell count <150/microliter[31].

From 1984 to 2010, a retrospective study was conducted on pediatric patients diagnosed with histoplasmosis in Colombia. A total of 45 cases were identified, with malnutrition being the most important risk factor, followed by environmental exposure. Pulmonary infiltrates were observed in 83% of patients, and 64% presented with a progressive disseminated form, frequently involving the central nervous system (48%)[37].

Clinically, it can present in three forms: acute, subacute, and chronic, differing not only in the duration of symptoms, but also in clinical presentation, histopathology, and diagnostic test performance[29.]

Acute Form of Progressive Disseminated Histoplasmosis

The condition has a sudden onset with fever, malaise, weight loss, cough, diarrhea, and nonspecific skin and mucosal lesions, with less than 15 days of evolution at the time of consultation. On physical examination, hepatosplenomegaly and cervical lymphadenopathy are frequently present in 50% of patients. Laboratory findings include anemia in over 90% of cases, bicytopenia or pancytopenia, inversion of plasma protein ratios (albumin/globulin ratio), and radiological evidence of interstitial infiltrates in 73.5% of patients, although normal findings occur in 23.5% of cases[5,30,38].

Skin tests are inconsistent in this form, with a sensitivity of 3-55%. Antibodies were detected in 58% of patients, urinary antigen sensitivity reached 95%, and antigenaemia sensitivity was 86%. Histopathological studies do not show granuloma formation or imperfect granulomas, and fungal structures are abundant both intra- and extracellularly, allowing direct exa-

mination and culture to establish the diagnosis in 60-90% of cases, and in 75% of blood and bone marrow samples. Molecular tests are occasionally used with a sensitivity of 95%[29,39].

Subacute Form of Progressive Disseminated Histoplasmosis

This form presents with symptoms lasting 1-2 months, including general malaise, fever, and weight loss. Its main characteristic is focal involvement in different organs, primarily the gastrointestinal tract, as evidenced by endoscopic examination in 40% of the cases. Adrenal gland involvement is also common, observed in 80% of autopsies, although glandular insufficiency is seen in only 10% of cases. It may also present with central nervous system involvement, manifesting as chronic meningitis, encephalitis, or nodular lesions[40]. In prosthetic or previously damaged heart valves, particularly the aortic and mitral valves, endocarditis may occur with generally negative blood cultures, making diagnosis difficult[29].

Chronic Form of Progressive Disseminated Histoplasmosis

This form occurs in patients with less severe immune compromise, with symptoms persisting for 3-6 months, including general malaise, weight loss, and occasional nondaily fever. In half of the patients, a deep, nonpainful oropharyngeal or genital ulcer can be identified, which may be mistaken for squamous cell carcinoma[1, 17.] It may also present with hepatosplenomegaly and occasionally granulomatous hepatitis, which can complicate pharmacological therapies. Severe cases may present with hemophagocytic syndrome, which has a mortality rate approaching 100%[29, 30, 41].

Rare Complications of Progressive Disseminated Histoplasmosis

Multisystem involvement with the development of complications is rare but is associated with high mortality. In patients with HIV infection, survival depends on CD4 T-cell count, with a lower count indicating a higher risk of death. In Colombia, mortality in this patient group has been reported in 23-33% of cases, contrasting with up to 48% in some regions of Brazilp'[42].

Adrenal insufficiency originates from the replacement of normal glandular tissue with granulomatous tissue with or without necrosis. It should be considered in patients presenting with orthostatic hypotension, hyponatremia, hyperkalemia, and marked eosinophilia. When adrenal insufficiency is present, it does not reverse with antifungal treatment and lifelong corticosteroids may be required[4,29].

Endovascular involvement is infrequent and should be suspected if signs of endocarditis are present, especially when there is structural cardiac damage or prosthetic valves. Blood cultures are positive in approximately 50% of patients and intracellular yeast can be observed in peripheral blood smears. In this case, urinary and serum antigen tests were of great value, but clinical suspicion was crucial[5].

Central nervous system involvement occurs in less than 10% of patients with subacute progressive disseminated histoplasmosis. Neurological symptoms are nonspecific and can be confused with those of tuberculous meningitis. The most common symptoms include headaches, confusion, and focal neurological deficits. Patients exhibiting this rare presentation are those with immune compromise and multisystem involvement; immunocompetent patients may only manifest isolated chronic meningitis[29].

Cerebrospinal fluid (CSF) cultures were positive in only 30% of cases. Measurement of urinary antigens has become the cornerstone for diagnosing this clinical presentation (sensitivity 95%), and the detection of antibodies in both CSF and peripheral blood increases the diagnostic probability (sensitivity of CSF antibodies 66%)[5, 30].

Evaluation

A high level of suspicion is imperative for diagnosing this disease, along with a thorough investigation of epidemiological history, although the location of exposure is difficult to identify in non-endemic regions[30]. The diagnosis should be suspected in patients with clear risk factors in endemic areas, such as children under two years old, elderly individuals, patients with immune alterations, or HIV-infected patients, especially those with AIDS, who present with typical manifestations of the disease, including fever, fatigue, and weight loss, although the spectrum of symptoms and signs depends on the affected organs[4].

Physical examination may reveal peripheral lymphadenopathy, visceromegaly, mucocutaneous lesions, or neurological abnormalities. Additionally, common laboratory abnormalities include anemia, bicytopenia (leukopenia and thrombocytopenia), elevated transaminase levels, alkaline phosphatase and/or bilirubin, LDH, and systemic inflammation biomarkers such as ferritin[24, 43]. In meningeal forms, CSF cytochemistry is nonspecific, with possible findings of lymphocytic pleocytosis, elevated protein levels, and hypoglycorrhachia[29].

Diagnosis

The gold standard for diagnosing histoplasmosis is the isolation of the fungus in culture and the histopathological examination of tissue biopsies, secretions, or body fluids. Table 1 presents the sensitivity of different diagnostic tests for histoplasmosis, considering the various clinical forms of the disease. The following tests are available for diagnosis[44].

Direct Examination and Histopathology

Wright staining, Gomori Methenamine Silver (GMS) staining, or periodic acid-Schiff (PAS) staining of tissue samples from mucocutaneous lesions, respiratory samples, or peripheral blood smears (Figure 1) can show intracellular yeasts in macrophages, measuring 2 to 4 micrometers. However, because of their structure, they are difficult to differentiate from other agents, such as Leishmania, making this technique not ideal for diagnosis but useful for guiding initial therapy in patients

with severe disease. In patients with progressive disseminated forms, the fungus can be seen in bone marrow, lymph node, liver, skin, and mucosal samples, and in severely ill individuals, yeasts can be observed in circulating phagocytic cells in peripheral blood, with a sensitivity of 20% in acute pulmonary forms, 75% in chronic pulmonary forms, and 76% in progressive disseminated forms[45,46,47].

Sensitivity and specificity are operator-dependent, which limits examination[48].

Culture

The isolation of *H. capsulatum* from clinical samples in culture media is considered the gold standard for diagnosis[44, 45]. Cultures were performed on standard fungal media, such as Sabouraud dextrose agar, which was incubated at 25°C. At this temperature, the fungus grew as a mold, appearing white to pale yellow. It has a slow growth rate (between 4-6 weeks), which does not allow for the timely initiation of specific treatment[44, 45]. A laboratory requires a high level of security (biosafety level 3). The sensitivity is around 70%, depending on the clinical form, with lower rates in acute pulmonary forms (10-49%), intermediate in chronic pulmonary forms (17-50%), and higher in disseminated forms (76%)[44,49,50].

Identification is based on the macroscopic and microscopic characteristics of the fungus in its filamentous phase and demonstration of its dimorphism in vitro[5, 44]. In a recent study published by Cáceres et al. (2019), the overall sensitivity of culture-based diagnosis in patients with HIV was approximately 77%. It was also demonstrated that cultures from respiratory samples have lower yields than bone marrow or blood cultures; the latter increases their sensitivity in patients with severe disseminated disease, especially if they have some form of immune defect. Sensitivity is higher in blood samples if lysis centrifugation is used for culturing[49].

Antibody Detection

Antibody tests are useful for diagnosing and monitoring the treatment of histoplasmosis, although each patient must be individualized[39,40]. The two most commonly used tests are agar gel immunodiffusion (AGID) and complement fixation (CF). Complement-fixing antibodies target two antigens of *Histoplasma* (mycelial and yeast phases: histoplasmin) and appear 3–6 weeks after infection with the fungus in up to 95% of patients, persisting for years. A titer greater than or equal to 1:32 or a fourfold increase in titers provides strong diagnostic evidence of acute, chronic, and disseminated infection[44].

This assay is less sensitive and specific than immunodiffusion, which qualitatively analyzes the H and M bands (precipitins) in the serum and cerebrospinal fluid. The sensitivity and specificity of immunodiffusion are around 80% in immunocompetent patients, decreasing to 50-60% in immunocompromised individuals, as this latter group is unable to generate an adequate cellular response[44,45,51,52]. The M band appears with acute infection and is also present in chronic forms, often persisting when the infection resolves. The H band appears after the M band, but is more related to subacute and chronic infections and rarely appears in isolation. However, most cases in which both are present indicate an active infection. The simultaneous use of AGID and CF increases the diagnostic probability[30,44].

The difficulty in interpretation lies in the fact that cross-reactions occur with paracoccidioidomycosis, blastomycosis, coccidioidomycosis, tuberculosis, and sarcoidosis[53]. Currently, immunoassays and Western blot are available to detect IgG and IgM antibodies, with sensitivity and specificity around 60-85%, but they are not commercially available[44,45,54].

The challenge in its interpretation lies in the occurrence of cross-reactions between paracoccidioidomycosis, blastomycosis, coccidioidomycosis, tuberculosis, and sarcoidosis[53]. Currently, immunoassays and Western blot are available for detecting IgG and IgM antibodies, with a sensitivity and specificity of 60-85%, but these are not commercially available in most endemic countries[44,45,54].

Another limitation is the need for specialized laboratories to perform CF, which is not always possible in all clinical settings. This has led to other tests, such as enzyme immunoassays (EIA), which are preferred because of their speed and ease of use[44,45.] Miravista Diagnostics developed an enzyme immunoassay (EIA) that offers higher sensitivity than current antibody tests, while allowing the separate detection of IgG and IgM antibodies and complementing antigen detection. This combination provides the optimal method for diagnosing acute pulmonary histoplasmosis[55].

Table 1. Sensitivity of different tests for the diagnosis of histoplasmosis

	Acute Pulmonary	Subacute Pulmonary	Chronic Pulmonary	Meningeal	Progressive Disseminated
Microscopy	0-47%	9-67%	10-75%	-	12-85%
Culture	0-34%	9-82%	65-85%	19-33%	75-92%
Antibodies	40-80%	78-92%	65-100%	60-90%	58-75%
Antigens	43-65%	40%	25-80%	42-78%	90-98%
NAAT	50%	-	-	33%	95%

Modified from Toscanini et al. (2021)[39].
NAAT: nucleic acid amplification test.

Detection of Fungal Antigens

This test detects galactomannan antigen, which is a crucial component of the fungal cell wall. It has become an important test for diagnosing the disease due to its speed and ease of execution; in children, it is particularly valuable as it has a better performance than in adult patients[4, 30, 44]. Detection of this antigen was first developed in 1986 and is currently a quantitative enzyme-linked immunosorbent assay (ELISA) that can be used in urine, serum, BAL, and other sterile body fluids such as CSF[44].

Acute pulmonary histoplasmosis has a sensitivity of 65%, and in progressive disseminated forms, 95%, especially if the microbial load is high, such as in children, immunosuppressed patients, or those with HIV infection[44, 45]. Antigen measurement can also be useful for monitoring treatment progress, as antigen levels decrease with therapy until they become undetectable, persisting at elevated levels in therapeutic failure[56]. Increases of more than four units at the end of treatment are associated with disease relapse. Cross-reactions occur with *B. dermatitidis* and other endemic tropical mycoses, such as paracoccidioidomycosis, coccidioidomycosis, aspergillosis, and *T. marneffei* infection[44, 57].

In recent years, MiraVista Diagnostics developed a lateral flow immunochromatographic test for visual detection of urinary antigens, with results available in less than an hour and sensitivity and specificity greater than 95%. In a study conducted in Colombian patients with HIV/AIDS, the test showed high performance using an automatic reader for serum samples, with sensitivity values close to 95%[58].

Polymerase Chain Reaction and Nucleic Acid Amplification (PCR)

Molecular methods for the diagnosis of histoplasmosis have been reported in several commercial laboratories. This could help with rapid and specific identification from infected biological samples or from the filamentous phase observed in cultures. PCR allows for the identification of different species of *Histoplasma*, and real-time PCR (PCR-TR) and nested PCR are sensitive and specific tests for respiratory and bronchial aspirate samples, particularly in individuals with HIV infection[44]. Only 2.5-3 ml are required, treated with lyticase extracted from *Trichoderma harzianum* and proteinase K to improve performance[13]. The sensitivity was 95%, with a specificity of 99%[49, 56]. However, it is not widely used because of the lack of methodological consensus and absence of a commercial kit.

Molecular detection of histoplasmosis by polymerase chain reaction (PCR) using the Hcp100 molecular marker is a promising approach for diagnosing this fungal infection. The Hcp100 marker refers to a gene that encodes a 100 kDa protein specific to *Histoplasma capsulatum*, the causative agent of histoplasmosis[59].

The use of nested PCR targeting the Hcp100 gene has proven to be highly specific and sensitive for detecting *H. capsulatum* in clinical samples. One study evaluated the effectiveness of two nested PCR assays for detecting *H. capsulatum* DNA in human tissues and found that the assay targeting the 100 kDa protein gene showed 100% specificity without the need for additional sequencing, making it highly reliable in avoiding false-positive results[59].

Additionally, a loop-mediated isothermal amplification (LAMP) method has been developed that also utilizes the Hcp100 locus for detecting *H. capsulatum* DNA in clinical samples. This method demonstrated 100% sensitivity and specificity when tested with DNA extracted from *H. capsulatum* cultures and demonstrated the ability to detect fungal DNA in urine samples from patients with confirmed histoplasmosis[60].

Treatment

The treatment must be individualized because, in a previously healthy and immunocompetent host, the disease is usually self-limiting, and treatment may not be necessary. In 2007, the Infectious Diseases Society of America (IDSA) published guidelines on the treatment of histoplasmosis, which remain valid today. These guidelines indicate that in mild to moderate acute pulmonary infections with symptoms lasting less than four weeks in immunocompetent patients, treatment is generally not required, as the immune system usually eliminates the infection without sequelae[61,62].

However, treatment should be considered in all diagnosed cases to prevent the fungus from persisting in a latent form and its potential reactivation later when the immune system is altered. In mild to moderate diagnosed cases, itraconazole 200 mg/day is recommended for three months in adults or 5 mg/kg/day in pediatric patients (not exceeding the adult dosage)[62]. It is essential to individualize treatment in immunocompromised patients, who always require treatment because infection dissemination is likely to progress unchecked[62].

In all severe pulmonary forms, amphotericin B deoxycholate should be initiated at doses of 0.7-1 mg/kg/day for 4-6 weeks or until clinical improvement, or in its liposomal forms at doses of 3-5 mg/kg/day, always followed by oral itraconazole 200 mg three times a day for three days as a loading dose to achieve therapeutic levels early on, and then twice a day for one year. In children, the dose of itraconazole is 5-10 mg/kg/day (maximum 400 mg/day)[45, 61, 62]. In chronic pulmonary forms, treatment is required for 18 to 24 months to prevent relapses[45,61,62].

In patients with progressive disseminated forms, treatment begins with liposomal amphotericin B at doses of 3-5 mg/kg/day until improvement or at least for 2–4 weeks, followed by oral itraconazole at a dose of 400 mg/day in adults or 5-10 mg/kg/day in pediatric patients for 12 months. For severe forms of progressive disseminated histoplasmosis (PDH), the IDSA recommends liposomal formulations of amphotericin

B over deoxycholate forms because they show better therapeutic outcomes (82% vs. 56%, respectively) and fewer adverse effects, particularly renal effects. However, in patients at low risk of nephrotoxicity, amphotericin B deoxycholate may be used under laboratory monitoring[61,62,63].

In patients with PDH and HIV infection, treatment guidelines have been recently updated[64]. In cases of central nervous system involvement, the indicated treatment is liposomal amphotericin B at a dose of 5 mg/kg/day, followed by itraconazole for one year or more, considering the normalization of CSF findings. The use of new azole compounds, such as voriconazole, which achieve better concentrations in the CSF, constitutes an alternative in these cases[4,61]. Another option is posaconazole, which has less drug interaction with other necessary simultaneous treatments such as anti-TB and ART[65].

Follow-Up

Mycological and clinical cures should be sought to reduce the probability of disease relapse, especially in immunosuppressed or HIV-infected patients. Antigenuria should be measured using enzyme immunoassay to evaluate treatment; this should be quantified at baseline, at two weeks or at the time of switching from amphotericin B to itraconazole, at four weeks, and then every three months throughout the course of treatment. Ideally, the levels should be below 4 U/ml or negative, considering that the treatment durations described above should be adhered to[62].

In conclusion, histoplasmosis is the most common endemic mycosis in America. In its progressive disseminated form, it causes thousands of deaths in the Americas, especially in people with HIV/AIDS or pediatric patients. Exposure to organic material rich in birds and bat guano is an important factor for diagnosis. A high level of suspicion is necessary, given the increasing number of patients undergoing immunosuppressive treatments or with immune defects. This issue is of great importance because of the difficulty in establishing a diagnosis, particularly in low-income countries, and considering that it is a potentially treatable infection with a favorable outcome in those who receive timely diagnosis and treatment.

Ethical considerations

Protection of persons. The authors declare that no experiments involving humans or animals were conducted in this narrative review.

Protection of vulnerable populations. Not applicable.

Confidentiality. Not applicable, as no access to medical records was required due to the nature of the manuscript.

Privacy. Not applicable.

Financing. The authors declare that this manuscript has been solely funded by the authors' own resources.

Conflict of interests. The authors have no conflict of interest to declare.

Acknowledgments. To the staff of the Colombian Institute of Tropical Medicine (ICMT-CES) for their encouragement in carrying out this manuscript.

Authors´ contribution. M.M, A.T: conceptualization; M.M, N.R: research and methodology; M.M, N.R: manuscript writing; M.M, A.T: critical revision and editing of the manuscript. All authors contributed to read and approved the version of the submitted manuscript.

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